Efficacy and Safety of Riluzole in Acute Spinal Cord Injury (SCI). Rationale and Design of AOSpine Phase III Multi-center Double Blinded Randomized Controlled Trial. (RISCIS).

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Background

Over 1 million people living with Spinal Cord Injury (SCI) in North America alone. Annual costs for the acute treatment and chronic care of these patients totaling four billion dollars USD. Beyond supportive care, there are no medical or surgical treatments that have been clearly demonstrated to improve functional outcome in human SCI.

Phase I/IIa Riluzole Trial

The primary aim: To develop acute care safety and pharmacokinetic profiles of riluzole in patients who have sustained a traumatic spinal cord injury
Secondary objectives: To conduct exploratory analyses of neurological outcomes for purposes of planning a subsequent Phase II b – Phase III randomized study of the efficiency of riluzole for the treatment of acute spinal cord injury

Patient Characteristics

Characteristic	Patient Number N=36
Gender:	
Male	30 (83%)
Female	6 (17%)
Mean Age	39 (Min:18 Max:69)
Neurological Level of Injury:	
Cervical	28 (78%)
Thoracic	8 (22%)
ASIA Impairment Scale (AIS) grade:	
AIS grade A	19 (53%)
AIS grade B	9 (25%)
AIS grade C	8 (22%)
Etiology:	
Motor Vehicle Accident	20(55%)
Fall	9(25%)
Sport related	5(14%)
Assault	2 (6%)

	Riluzole N = 36		Registry N = 36		
System/Category	Patients[1]	Incidence[2]	Patients[1]	Incidence[2]	P-value[3]
Infection	14	0.389	13	0.361	**0.81**
Pulmonary	11	0.306	16	0.444	**0.22**
Neuropsychiatric	10	0.278	10	0.278	**1.00**
Hematological	7	0.194	9	0.250	**0.57**
Cardiovascular	5	0.139	11	0.306	**0.09**
GI/GU	5	0.139	9	0.250	**0.19**
Skin	4	0.111	3	0.083	**0.69**

Phase I/IIa Trial: Conclusion

Have established feasibility of a multicenter trial evaluating Riluzole in traumatic SCI
Preliminary safety and neurological recovery data appear promising

Methods

This Phase II/III multi-center double-blind randomized controlled trial will involve up to 35 sites. A total of 351 patients with acute C4—C8 SCI and ASIA Impairment Grade A, B or C will be randomized 1:1 to riluzole and placebo. Primary outcome is the change in ASIA Total Motor Score between baseline and 180 days. Other measures include ASIA Upper Extremity Motor Score; ASIA Lower Extremity Motor Score; ASIA Sensory Score; ASIA grade; Spinal Cord Independence Measure); SF-36v2; EQ-5D and GRASSP. The statistical design utilizes 2-stage sequential adaptive trial. A sample size of 316 subjects (158 in each arm) will have 90% power to detect 9 points difference in the ASIA Motor Score at one-sided alpha = .025. To account for losses to follow-up of up to 10%, the study will enroll 351 subjects.

Statistical Design

Sample size of 316 evaluable subjects will have 90% power to detect .37 Cohen's d effect size (i.e. 9 difference in ISNCSCIMS). There is no published minimally significant difference for ISNCSCIMS. The current effect estimate of 9 is arbitrarily set. Study uses adaptive sequential design that allows sample size change during the interim analysis. In order to account for loss of power due to loss of follow-up and possible adjustments for baseline factors we will increase sample size by 10% to 351 enrolled subjects.

Plan ID	Parameter
Type of the hypothesis	1-Sided
Type I Error (α)	0.025
Power (1 - β)	0.90
Randomization Ratio (Investigational vs. Control)	1:1
Planned Number of Interim Looks	2
Spacing of Looks	60%, 100%
Hypothesis to be Rejected	H0 or H1 (binding)
Boundary Family	Published Function
Boundary to Reject H0	O'Brien-Fleming
Boundary to Reject H1	Gamma (-1)
Difference of Means Assuming H_1	9
Standard Deviation (σ)	24.08
Sample Size	316 (158 per arm)

Current Status

Subject enrollment to begin October 2013

Study Design

Primary outcome measure is change in ISNCSCI Total Motor Score between baseline and 180 days following enrollment.
Secondary outcomes measures include ISNCSCI grade, ISNCSCI Sensory Scores, SCIM, SF-36v2, EQ-5D, GRASSP, Pain NRS

Results

Within the Phase 1 study a matched cohort analysis was performed comparing complication rates and neurological outcomes between patients who received riluzole and matched non-riluzole treated patients from a prospective SCI registry. Although the groups experienced similar rates of complications, riluzole treated cervical SCI patients experienced an additional 15.5 points in AMS recovery at 90 days post injury as compared to non-riluzole treated patients. Although the phase I study was underpowered to investigate efficacy the current phase II/III study is poised to definitive address this question. Subject enrollment for this trial began October 1, 2013.

Conclusions

This is a pivotal study of riluzole in acute SCI.

Acknowledgements